510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
DEVICE ONLY TEMPLATE

A. 510(k) Number: K032049

B. Analyte: Valproic Acid

C. Type of Test: quantitative chemistry

D. Applicant: Roche Diagnostics

E. Proprietary and Established Names: Roche Online TDM Valproic Acid Assay

F. Regulatory Information:

1. Regulation section: 21 CFR 862.3645

2. Classification: Class II

3. Product Code: LEG

4. Panel: 91

G. Intended Use:

1. Intended use(s): For the quantitative determination of valproic acid in human serum or plasma on automated clinical chemistry analyzers.

2. Indication(s) for use: The Roche Online TDM Valproic Acid assay contains an in vitro diagnostic reagent system indicated for the quantitative determination of valproic acid in human serum or plasma on automated clinical chemistry analyzers. Valproic acid is primarily used in the treatment of petit mal seizures and other generalized and partial complex seizures.

3. Special condition for use statement(s): none stated

4. Special instrument Requirements: Roche/Hitachi 911, 912, 917 and Modular P clinical analyzers

H. Device Description: The Roche Online TDM Valproic Acid assay contains an in vitro diagnostic reagent system indicated for the quantitative determination of valproic acid in human serum or plasma on automated clinical chemistry analyzers.

I. Substantial Equivalence Information:

1. Predicate device name(s): Roche Valproic Acid II Assay

2. Predicate K number(s): K930734

3. Comparison with predicate:

Item	Device	Predicate
Fundamental method principle differs between the two assays	The assay is a homogenous immunoassay based on the principle of measuring changes in scattered light or absorbance which result when activated microparticles aggregate. The microparticles are coated with valproic acid antibody solution. When a sample containing valproic acid is introduced, the aggregation reaction is partially inhibited, slowing the rate of the aggregation process. Antibody bound to the sample drug is no longer available to promote microparticle aggregation, and subsequent particle lattice formulation is inhibited. Thus, a classic inhibition curve with respect to valproic acid concentration is obtained, with the maximum rate of aggregation at the lowest valproic acid concentration. By monitoring the change in scattered light or absorbance, a concentration-dependent curve is obtained.	The Valproic Acid II assay uses recombinant DNA technology to produce a unique homogenous enzyme immunoassay system. The assay is based on the bacterial enzyme beta-galctosidase, which has been genetically engineered into two inactive fragments. These fragments spontaneously reassociates to form a fully active enzyme that, in the assay format, cleaves a substrate, generating a color change that can be measured spectrophotmetrically.

J. Standard/Guidance Document Referenced (if applicable): NCCLS/EP5-T2,

K. Test Principle: The Roche ONLINE TDM Valproic Acid assay contains an in vitro diagnostic reagent system indicated for the quantitative determination of valproic acid in human plasma or serum. The calibrators and controls for this assay are sold separately.

L. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility: Reproducibility was determined using controls and human serum pools (HSP) in an internal protocol (modified version of NCCLS EP5-T2). Within run n=63, between day n=21, total n=63

	Within run			Between day			Total		
Sample	mean ug/ml	SD ug/ml	%cv	mean ug/ml	SD ug/ml	%cv	mean ug/ml	SD ug/ml	%cv
Control 1	34.8	0.29	0.8	34.7	0.80	2.3	34.8	0.73	2.1
Control 2	74.1	0.47	0.6	74.3	1.78	2.4	74.1	1.80	2.4
Control 3	118.9	0.73	0.6	119.0	2.22	1.9	118.9	2.21	1.9
HSP 1	55.6	0.34	0.6	55.7	1.94	3.5	55.6	1.95	3.5
HSP 2	119.8	0.74	0.6	120.1	2.61	2.2	119.8	2.60	2.2

b. Linearity/assay reportable range: To assess the linearity of the assay, an 11-level dilution series was prepared using a valproic acid spiked human serum pool diluted with a non-spiked human pool. Results were evaluated by linear regression. Established linear range is 4.3 – 152.4 ug/ml.

c. Traceability (controls, calibrators, or method): The COBAS-FP Valproic Acid calibrators are prepared to contain known quantities of Valproic Acid in normal human serum and are traceable to USP reference standards. These calibrators are used to create a standard curve from which the quantity of drug in unknown specimens can be determined.

d. Detection limit: The detection limit of the Valproic Acid assay is 4.3 ug/ml. The lower detection limit represents the lowest valproic acid concentration that can be distinguished from zero. It is calculated as the concentration lying two standard deviations above that of the 0 ug/ml calibrator (within run precision n=21).

e. Analytical specificity: Samples were spiked with 16 common drugs and tested for specificity. No significant interference with the assay was found. Acetyl cysteine, Acetylsalicylic Acid, Ampicillin-Na, Acetaminophen, Ascorbic Acid, K-Doesilate, Cefoxin, Cyclosporin, Doxycycline, Ibuprofen, Levodopa, Methyldopa+1,5, Metronidiazole, Phenylbutazone, Rifampicin, and Theophylline. The manufacturer states "As with any assay employing mouse antibodies, the possibility exists for interference by human anti-mouse antibodies (HAMA) in the sample, which cause falsely low results."

f. Assay cut-off: The assay measuring range is 4.3 – 140 ug/ml. Serum therapeutic levels are 50 – 100ug/ml while toxic levels are >150 ug/ml (based upon the Applied Therapeutic Drug Monitoring, Washington

D.C. , The American Association of Clinical Chemistry and Essentials of Therapeutic Drug Monitoring, Gerson,B., editor).

2. Comparison studies:

   a. Method comparison with predicate device: The Roche ONLINE TDM Valproic Acid was evaluated for several performance characteristics, including precision, lower detection limit, method comparison, specificity, and interfering substances. All of the evaluation studies gave acceptable results compared to the predicate device. The following represents the precision and method comparison results.

   Roche ONLINE TDM Valproic Acid vs. Roche Valproic Acid II Assay (predicate device) n=75, Y= 0.969X+3.003 R=0.992 Range of samples 11.3 – 144.2 ug/ml.

NCCLS Precision:	Level 1	Level 2	Level 3
Mean (ug/ml)	34.8	74.1	118.9
CV% (within run)	0.8	0.6	0.6
CV(%) (total)	2.1	2.4	1.9

   b. Matrix comparison: Reproducibility was determined using controls and human serum pools (HSP) in an internal protocol (modified version of NCCLS EP5-T2). Within run n=63, between day n=21, total n=63

	Within run			Between day			Total		
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HSP 1	55.6	0.34	0.6	55.7	1.94	3.5	55.6	1.95	3.5
HSP 2	119.8	0.74	0.6	120.1	2.61	2.2	119.8	2.60	2.2

3. Clinical studies:

   a. Clinical sensitivity: none stated

   b. Clinical specificity: none stated

   c. Other clinical supportive data (when a and b are not applicable):

4. Clinical cut-off: none stated

5. Expected values/Reference range: The assay measuring range is 4.3 – 140 ug/ml. Serum therapeutic levels are 50 – 100ug/ml while toxic levels are >150 ug/ml (based upon the Applied Therapeutic Drug Monitoring, Washington D.C. , The American Association of Clinical Chemistry and Essentials of Therapeutic Drug Monitoring, Gerson,B., editor).

M. Conclusion: Based upon the performance characteristics and correlation data supplied, I recommend that the Roche Online TDM Valproic Acid Assay be found substantially equivalent to the respective predicate device.